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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/526,372	OHIZUMI ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,13-18,21,22,24 and 26-32* is/are pending in the application.

4a) Of the above claim(s) *15,17,22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,13,14,16,18,21 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/05/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 09/14/2010, is acknowledged.

2. Claims 1, 2, 5-7, 9, 13-18, 21, 22, 24 and 26-32 are pending.

3. Claims 15, 17, 22 and 24 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1, 2, 5-7, 9, 13, 14, 16, 18, 21 and 26-32 are under consideration in the instant application as they read on the MRL/lpr (Fas mutation/SLE) mouse species.

5. Applicant's IDS, filed 05/05/2010, is acknowledged.

6. The following new ground of rejections are necessitated by the amendment submitted 09/14/2010.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 2, 5-7, 9, 13, 14, 16, 18, 21 and 26-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The recitations "the purified antibodies have a dissociation constant of 10^{-10}M" in claims 27-29 and "the purified IgG1 or IgG2b antibodies have a dissociation constant of 10^{-10}M" in claims 30-32, are indefinite. It is not clear whether the dissociation constant of 10^{-10}M refers to Fc-FcR or Fab-Ag complex interaction of the purified IgG1/IgG2b/antibodies.

B. The recitation "purifying IgG1, IgG2a, IgG2b, IgG3 and IgM antibodies" in claims 1, 2 and 7, is indefinite. It is not clear how all the specific isotypic variants of polyclonal antibodies would be purified.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 2, 5-7, 9, 13, 14, 16, 18, 21 and 26-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a *New Matter* rejection.

The phrase "purifying IgG1, IgG2a, IgG2b, IgG3 and IgM antibodies" claimed in claims 1, 2 and 7 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 09/14/2010 points to the specification at page 27, 2nd ¶ for support for the newly added limitations "the purifying IgG1, IgG2a, IgG2b, IgG3 and IgM antibodies" as claimed in claims 1, 2 and 7. However, the specification does not provide a clear support for such limitation. It is noted that the specification purified only clones (see Fig. 2 and page 27, lines 1-9) not isotypic variants of antibodies as claimed. The 2nd ¶ of page 27 discloses performing isotype analysis on the isolated clones. No purification of antibodies based on IgG1, IgG2a, IgG2b, IgG3 and IgM was contemplated in the specification. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 7, 9, 14, 16, 18, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,235,714, in view of Gharavi et al (Clin. exp. Immunol. (1989) 78, 233-238).

The `714 patent teaches six MRL/lpr mice were hyperimmunized with target antigen such as EGFR, TNFα, IL-1β among others (see fig. 19 and col., 8, under selection and preparation of CRAAs in particular) to drive the immune system to generate catalytic antibodies. Blood will be obtained from the retro-orbital plexus at ten day intervals (see col., 14, under immunization, col., 43, lines 56-66 in particular). The `714 patent teaches that target antigens listed in Fig. 19 such as Macrophage inhibitory factor (MIF), C5, GPIIb/IIIa receptor (96% at the amino acid level), FVII, IL-4, IL-5, IgE, Eotaxin, PDGF, αvβ3 integrin (96% at the amino acid level).The target antigen proteins listed in fig. 19 exhibit human native proteins which have an amino acid sequence homology 94 % or higher in the absence of evidence to the contrary. The `714 patent

further teaches that the MRL/lpr mouse strain, contain a mutation of the Fas apoptosis gene is believed to permit proliferation of T and B cells and expression of lupus-like disease (see col. 36, lines 63-65). The `714 patent teaches that the human antigen in the exemplary CRAA-IL1-β peptide (PKKKMEK) (see fig. 16) shares a native protein which has PKKKMEK sequence identity of 100% at the amino acid sequence level to the mouse protein antigen (see Exhibit A, under amino acid positions in the "Query" 90-97 provided in the previous Office Actions).

The `714 patent differs from the claimed invention by not express purifying IgG1, IgG2a, IgG2b, IgG3 and IgM antibody in claim 7,

However, Gharavi et al reported that IgG subclass analysis of these antibodies in 20 MRL/lpr sera revealed that all four subclasses were represented (see abstract). Further, Gharavi et al teach that although the presence of anti-phospholipid antibodies in autoimmune mice has been described in some reports, these antibodies were mostly polyspecific monoclonal IgM antibodies (see page 236, 1st ¶ under DISCUSSION). Gharavi et al teach that anti-cardiolipin and anti-DNA ELISAs were performed as described above, except that rabbit anti-mouse IgGl, IgG2a, IgG2b, and IgG3 were used as second antibodies. Each anti-serum was used at a 1: 1000 dilution since they produced equal ODs on ELISA plates coated with 1μg/ml of the corresponding purified monoclonal IgG subclass at this dilution (see Fig. 4 and page 234, under IgG subclass analysis).

Given that the MRL/lpr sera revealed all four IgG subclasses were represented in the sera, one skilled in the art at the time the invention was made would be motivated to determine the isotypic variations of the different monoclonal antibodies obtained from MRL/lpr mice which were hyperimmunized with target antigen.

Claims 29 and 32 are inherent properties of the isolated clones (monoclonal antibody) which may also depend on the antigen immunized.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Makino et al (J Clin Lab Immunol. 1988 Feb;25(2):83-8) and Lage et al (2001, IDS CA) and Gharavi et al (Clin. exp. Immunol. (1989) 78, 233-238).

The `390 publication teaches that a mouse having an autoimmune disease such as MRL/l mouse can be used to produce a monoclonal antibody (see the English translation provided by Applicant). The `390 publication teaches a method of producing a hybridoma which produces the monoclonal antibody, wherein an animal having an autoimmune disease is used as a mammal

from which plasma cells are obtained. It is preferable that the animal is selected considering the adaptability to myeloma used for cell fusion. A mouse or rat is preferable, wherein the mouse having an autoimmune disease includes N2B, NZW, B/WF1, MRL/l, BXSB male and SLN1 strain. A rat having an autoimmune disease includes a rat in which hypertension occurs spontaneously. Further, a normal mouse such as Balb/c of which the ability to produce autoantibodies increases by being administered with a polyclonal B cells activator such as lipopolysaccharide (LPS) of a gram negative bacterium and dextran sulfate and which is in the state of autoimmune disease may be used (see the Partial English translation of Japanese Publication No. 0104739).

The `198 patent teaches a preparation containing immunogens is used to immunize animals. Thereupon, the immunized animals are preferred to be selected with consideration of their compatibility with the myeloma used in cell fusion. Mice or rats are preferable. When using glycolipids which contain N-glycolylneuraminic acid, an object of this invention, animals with autoimmune disease are more preferable and mice with autoimmune disease are the most preferable. As the mice with autoimmune disease, there are NZB, NZW, B/WF1, MRL/l, BXSB (SLE) male, SL/Ni and other mice available. Normal mice such as Balb/c may be used as immunized animals if the mice become autoimmune by raising their autoantibody producing ability caused by the injection of a polyclonal B cell activator (PBA) such as bacterial lipopoly-saccharide (LPS) or dexstran sulfate (col. 8, lines 37-53 and claim 12 in particular). The `198 patent teaches that the glycolipids which contain N-glycolylneuraminic acid including gangliosides with the H-D antigen activity, one of the objects in this invention, are known to exist widely in mouse tissues, so that these glycolipids are autoantigens for mice. Therefore, these glycolipids are thought to have extremely weak immunogenicity. It is very difficult to obtain the monoclonal antibody specific to or against glycolipids containing N-glycolylneuraminic acid according to the conventional methods which use normal mice such as Balb/c mice as immunized animals. On the other hand, it is known that mice with autoimmune disease produce antibodies against autoantigens such as anti-nuclear antibodies or anti-erythrocyte antibodies (see col., 8, last ¶). The `198 patent teaches that the produced antibodies are very effective for study of cancer's occurrence mechanism diagnosis and treatment (see abstract in particular).

The claimed invention differs from the reference teachings only by the recitation that the mouse is Fas function defects and the antigen is glypican in claim 1 such as glypican-3 in claim 6 and purifying IgG1, IgG2a, IgG2b, IgG3 and IgM antibodies in claims 1-2 and 7.

Makino et al teach that comparative studies between male BXSB and MRL/lpr mice at the onset period. Makino et al teach that MRL/lpr mice had much higher level of serum IC than male BXSB mice at 13 weeks as assessed by fluid- and solid-phase C1q-binding assays (see abstract).

Lage et al teach that proteoglycans are glycoproteins containing various sulfated glycosaminoglycan residues, e.g., heparan sulfate. These glycoproteins, designated as heparan sulfate proteoglycans (HSPGs), are widely distributed in many tissues, occurring in various forms of extracellular matrices, at cell surfaces, and in intracellular granules. HS is a regulatory

polysaccharide. Glypicans, also called glypican-related integral membrane proteoglycans (GRIPS), are one of two major families of transmembrane HSPGs. The glypicans are anchored to membranes by a glycosyl-phosphatidylinositol (GPI) anchor. This covalently attached GPI residue was the source of the term glypican, which is derived from glycosylphosphatidylinositol-anchored proteoglycan (see page 438, under Introduction). Lage et al teach that despite many efforts, no mAb specifically recognizing the GPC3 polypeptide could be generated, it appears obvious that GPC3 is only weakly or not immunogenic in mice.

Claim 7 is included because human GPC3 has 94% sequence identity with the mouse.

However, Gharavi et al reported that IgG subclass analysis of these antibodies in 20 MRL/lpr sera revealed that all four subclasses were represented (see abstract). Further, Gharavi et al teach that although the presence of anti-phospholipid antibodies in autoimmune mice has been described in some reports, these antibodies were mostly polyspecific monoclonal IgM antibodies (see page 236, 1st ¶ under DISCUSSION). Gharavi et al teach that anti-cardiolipin and anti-DNA ELISAs were performed as described above, except that rabbit anti-mouse IgGl, IgG2a, IgG2b, and IgG3 were used as second antibodies. Each anti-serum was used at a 1: 1000 dilution since they produced equal ODs on ELISA plates coated with 1μg/ml of the corresponding purified monoclonal IgG subclass at this dilution (see Fig. 4 and page 234, under IgG subclass analysis).

Claims 27- 32 are inherent properties of the isolated clones (monoclonal antibody) which may also depend on the antigen immunized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb and identify the isotype variants of the mAb (as taught by Gharavi) against GPC3 using MRL/lpr mice autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390 publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144. The skilled in the art would be motivated to determine the IgG isotype variants and IgM of the mAb produced to determine their effect on the antigen specific antibody concentrations assigned to a reference mouse serum.

The skilled in the art would be motivated to use MRL/lpr mice because MRL/lpr would produce much higher level of serum IC than male BXSB mice.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 1-2, 5-7, 9, 13-14, 16, 18, 21 and 26-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP-01047390 (IDS ref. No. BB) OR US. Pat. No. 4,965,198 (IDS AA), each in view of Lage et al (2001, IDS CA), Gharavi et al (Clin. exp. Immunol. (1989) 78, 233-238) and U.S. Pat. No. 5,641,488.

The teachings of the `390 publication and the `198 patent, Lage and Gharavi et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the nonhuman animal that develops the autoimmune disease is Fas function defects in claims 1 and 7, the immunogen is glypican protein in claim 1 or a human native protein which has a sequence identity of 94% or more at the amino acid sequence level to a homolog protein of the mouse to be immunized in claim 7 and the mouse is the MRL/lpr mouse in claim 9.

The `488 patent teaches methods for producing an antibody which specifically binds to a chosen antigen using the so-called autoreactive animals, such as mouse strains NZBXSWR(F1) and MRL lpr/lpr (SLE model) animals may be used. "Autoreactive" animals do not require treatment to undergo B cell hypermutation. Such animals need only be immunized with the immunogen of choice when they are in an autoreactive state. Determination of when the animal is in such a state is easily determined by one skilled in the art (see col. 17, lines 23-30).

Lage et al teach that proteoglycans are glycoproteins containing various sulfated glycosaminoglycan residues, e.g., heparan sulfate. These glycoproteins, designated as heparan sulfate proteoglycans (HSPGs), are widely distributed in many tissues, occurring in various forms of extracellular matrices, at cell surfaces, and in intracellular granules. HS is a regulatory polysaccharide. Glypicans, also called glypican-related integral membrane proteoglycans (GRIPS), are one of two major families of transmembrane HSPGs. The glypicans are anchored to membranes by a glycosyl-phosphatidylinositol (GPI) anchor. This covalently attached GPI residue was the source of the term glypican, which is derived from glycosylphosphatidylinositol-anchored proteoglycan (see page 438, under Introduction). Lage et al teach that despite many efforts, no mAb specifically recognizing the GPC3 polypeptide could be generated, it appears obvious that GPC3 is only weakly or not immunogenic in mice.

Claim 7 is included because human GPC3 has 94% sequence identity with the mouse.

The limitations of claims 13 and 14 are inherent to the MRL/lpr mouse.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use MRL lpr/lpr taught by the `488 patent in a method for producing an antibody to GPC3.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make mAb against GPC3 using MRL/lpr mice autoimmune mice. The teachings of Lage et al pertaining to the difficulties in generating mAb specifically recognizing the GP3 polypeptide because GPC3 is only weakly or not immunogenic in mice and the teachings of the `390 publication and `198 patent indicating success in generating specific antibody in the face of having to solve a similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such animals need only be immunized with the immunogen of choice when they are in an autoreactive state (i.e., the MRL/lpr mouse need not to be induce with PBA to become autoreactive, spontaneous autoreactive).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 23, 2010

/Maher M. Haddad/
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